Neurocentro della Svizzera Italiana
Neurocenter of Southern Switzerland

ALS -
Nouvelles de la recherche

ALS-Tag, Bern, 23.6.22

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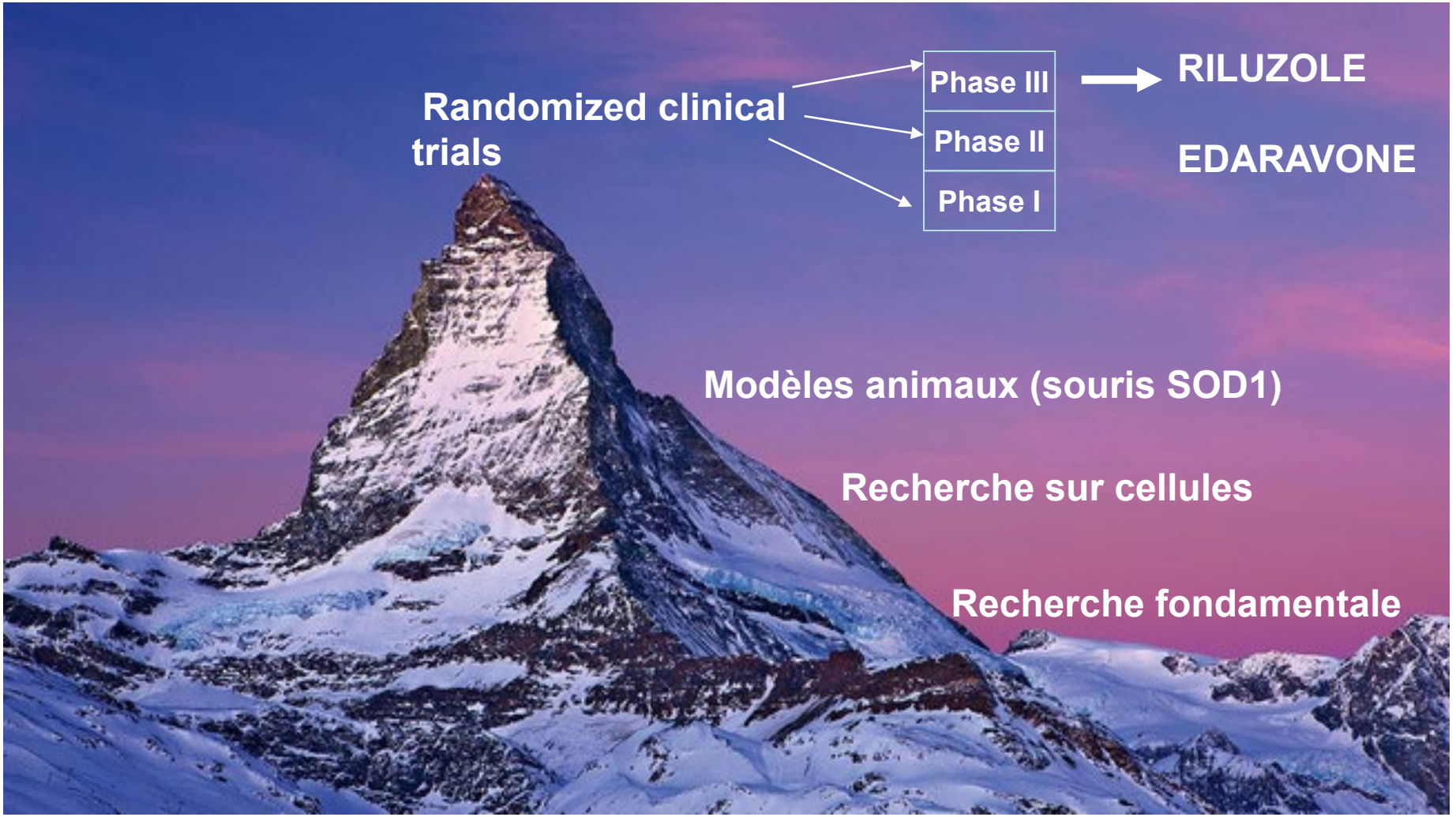
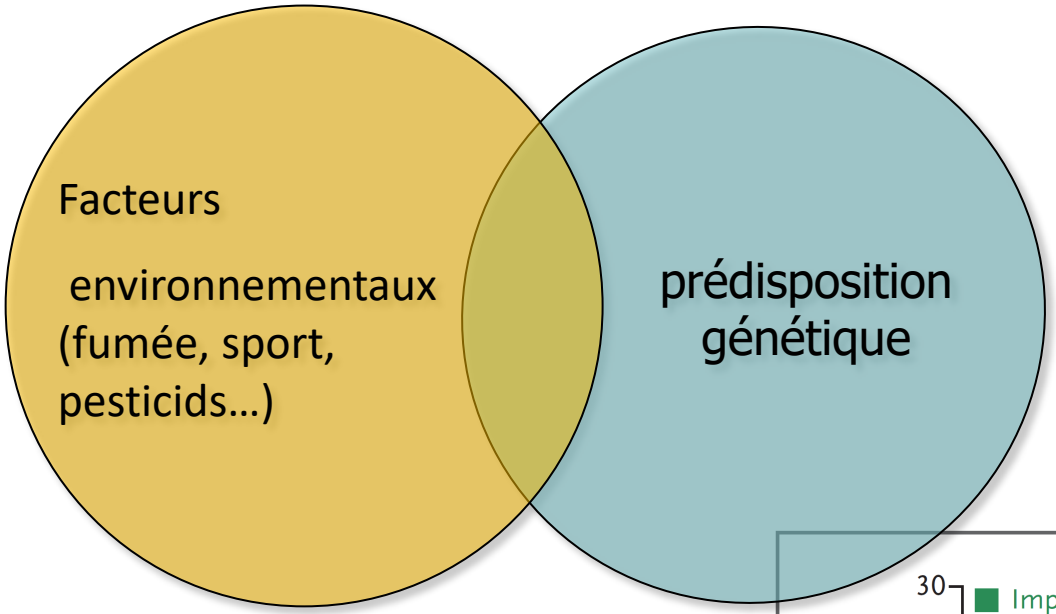
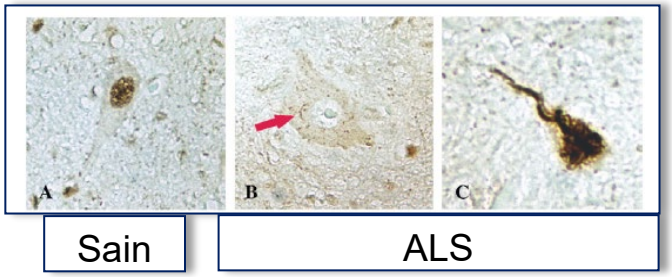
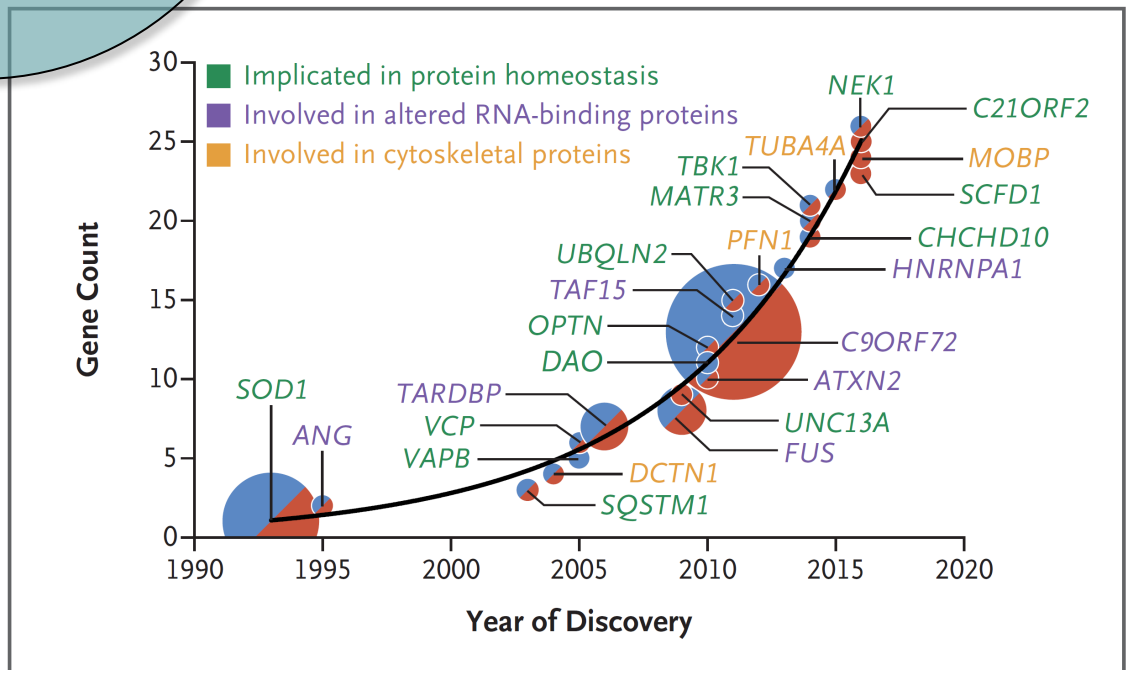
Nouvelles thérapies





TDP-43 protein





Brown RH, N Engl J Med. 2017

Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials

Leonard H. van den Berg, MD, PhD, Eric Sorenson, MD, Gary Gronseth, MD, Eric A. Macklin, PhD, Jinsy Andrews, MD, Robert H. Baloh, MD, PhD, Michael Benatar, MD, PhD, James D. Berry, MD, Adriano Chio, MD, Philippe Corcia, MD, PhD, Angela Genge, MD, Amelie K. Gubitz, PhD, Catherine Lomen-Hoerth, MD, PhD, Christopher J. McDermott, MD, Erik P. Pioro, MD, PhD, Jeffrey Rosenfeld, MD, PhD, Vincenzo Silani, MD, Martin R. Turner, MBBS, PhD, Markus Weber, MD, Benjamin Rix Brooks, MD, Robert G. Miller, MD, and Hiroshi Mitsumoto, MD, DSc, for the Airlie House ALS Clinical Trials Guidelines Group

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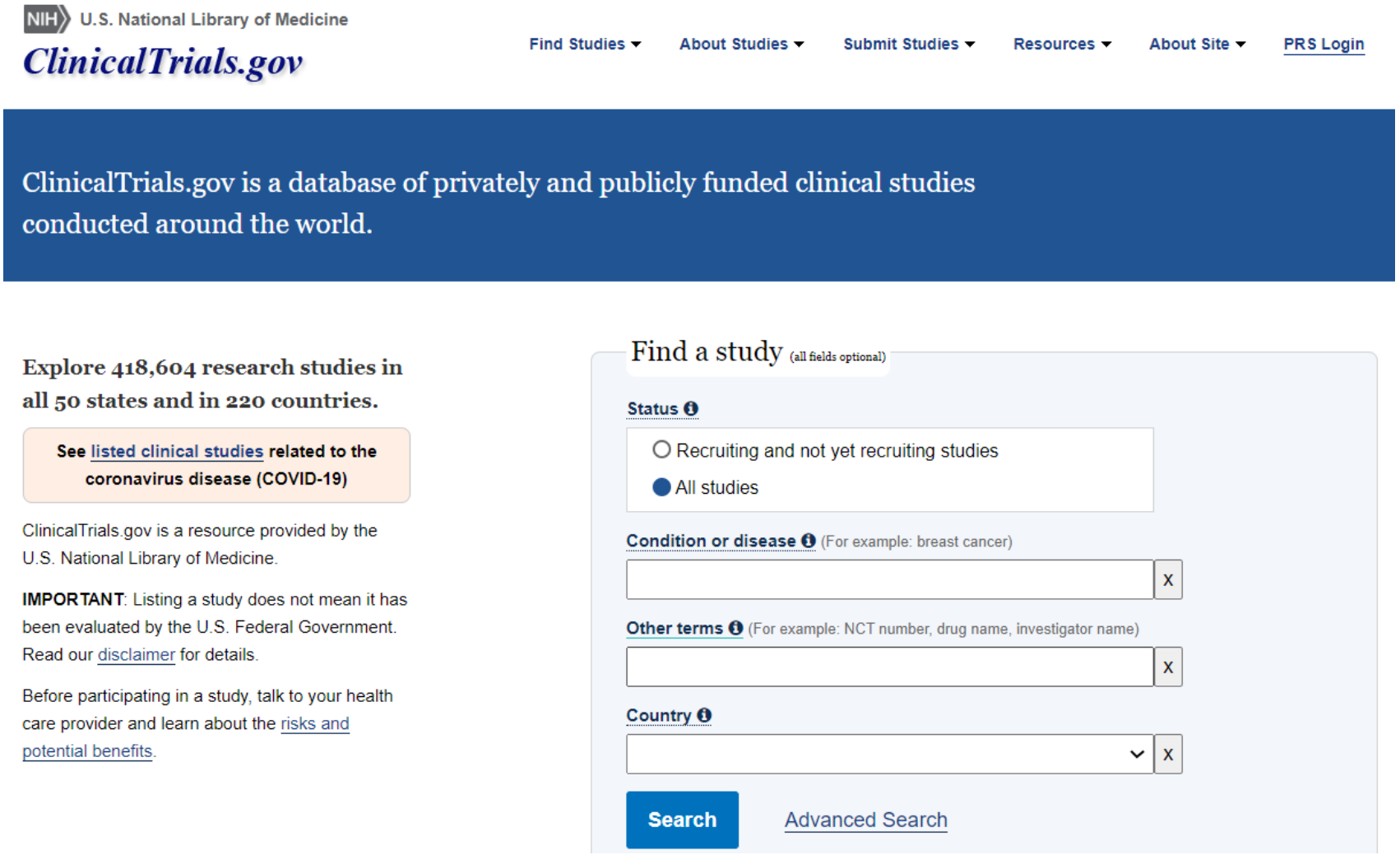
Neurology 2019 Apr 2;92(14):e1610-e1623

- Investigators should preferentially enroll PALS with "clinically definite," "clinically probable," "probable-laboratory supported," and "clinically possible" ALS, who have a short interval from disease onset to trial entry.
- Investigators should stratify for genetic factors and cognitive (especially executive function) and behavioral impairments.
- *Investigators should collect DNA from all participants, when possible, to allow genetic post hoc analyses, which may reveal important stratification or screening factors for a subsequent clinical trial(s).
- Investigators should choose to stratify for factors most relevant to the outcome measure of the trial.
- Investigators could stratify based on prognostic systems or prediction models.

Guidelines

- *Investigators should ensure ALS clinical trial results are published in open access journals.
- All efforts should be made to improve trial design in ways that expand the number of PALS receiving the experimental therapy, including limiting use of a placebo arm.
- Investigators should explain to PALS that withdrawing from clinical trials may reduce the certainty of results.
- Because safety and efficacy of experimental drugs are not demonstrated in phase 1 clinical trials, drug developers should move as quickly as possible to subsequent phase 2 trials where more reliable data on these parameters are obtained.



Filtres (e.g. «only phase III», «recruiting» etc.)

Approche génique

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Available	Expanded Access Program for **Tofersen** in Participants With **Superoxide Dismutase 1**-Amyotropic Lateral Sclerosis	• **Superoxide Dismutase 1**-Amyotropic Lateral Sclerosis	• Drug: **Tofersen**
2	☐	Completed	An Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of BIIB067 in Adults With Inherited **Amyotrophic Lateral Sclerosis** (**ALS**)	• **Amyotrophic Lateral Sclerosis**	• Drug: BIIB067 • Other: Placebo
3	☐	Recruiting	A Study of BIIB067 When Initiated in Clinically Presymptomatic Adults With a Confirmed **Superoxide Dismutase 1** Mutation	• **Amyotrophic Lateral Sclerosis** Associated With a **SOD1 Gene** Mutation	• Drug: BIIB067 (**Tofersen**)

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	A Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of ION363 in **Amyotrophic Lateral Sclerosis** Participants With **Fused in Sarcoma** Mutations (**FUS-ALS**)	• **Amyotrophic Lateral Sclerosis**	• Drug: ION363 • Drug: Placebo

- Jacifusen (ION363) actif sur FUS
- Phase 1-3

Stress oxydatif

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	Radicava® (Edaravone) Findings in Biomarkers From **ALS** (REFINE-**ALS**)	• **Amyotrophic Lateral Sclerosis** • **ALS**	• Drug: **Edaravone**
2	☐	Recruiting	Efficacy and Safety Extension Study of Oral **Edaravone** Administered in Subjects With **ALS**	• **ALS**	• Drug: MT-1186 • Drug: Placebo
3	☐	Recruiting	Efficacy and Safety Study of Oral **Edaravone** Administered in Subjects With **ALS**	• **ALS**	• Drug: MT-1186 • Drug: Placebo

Apoptose (mort neuronale)

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	Safety and Efficacy of **TUDCA** as add-on Treatment in Patients Affected by **ALS**	• **Amyotrophic Lateral Sclerosis (ALS)**	• Drug: **Tauroursodeoxycholic Acid** • Drug: Placebo

- TUDCA+Phenylbutirrate (Amx0035), Phase 3
- Soit Phenylbutirrate soit TUCDA avaient déjà été étudiés de manière isolée (et non en combinaison): Cudkowicz ME et al., Amyotroph Lateral Scler. 2009 Apr;10(2):99-106. ; Elia AE et al., Eur J Neurol. 2016 Jan;23(1):45-52
- Puis en phase 2 en association (3 g de phénylbutyrate de sodium et 1 g de taurursodiol, une fois par jour pendant 3 semaines, puis deux fois par jour) pendant 24 semaines : Paganoni S et al, N Engl J Med. 2020 Sep 3;383(10):919-930. -> Différence dans la baisse du score ALSFRS-R de 0,42 points par mois

Neuro-inflammation

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Completed	**Masitinib** in Combination With Riluzole for the Treatment of Patients Suffering From **Amyotrophic Lateral Sclerosis** (**ALS**)	• **Amyotrophic Lateral Sclerosis** (**ALS**)	• Drug: **Masitinib** (4.5) • Drug: Riluzole • Drug: Placebo • Drug: **Masitinib** (3.0)
2	☐	Recruiting	Efficacy and Safety of **Masitinib** Versus Placebo in the Treatment of **ALS** Patients	• **Amyotrophic Lateral Sclerosis**	• Drug: **Masitinib** (6.0) • Drug: Riluzole • Drug: Placebo • Drug: **Masitinib** (4.5)

Masitinib, Phase 3; actif sur les mastocytes

Autres mécanisms

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	A Study to Evaluate the Efficacy and Safety of **Reldesemtiv** in Patients With **Amyotrophic Lateral Sclerosis** (**ALS**)	• **Amyotrophic Lateral Sclerosis**	• Drug: **Reldesemtiv** • Drug: Placebo
2	☐	Completed Has Results	A Study to Evaluate Efficacy, Safety and Tolerability of CK-2127107 in Patients With **Amyotrophic Lateral Sclerosis** (**ALS**)	• **Amyotrophic Lateral Sclerosis**	• Drug: **Reldesemtiv** • Drug: Placebo

- Reldesemtiv (COURAGE-ALS, Phase 3)
- Il s'agit d'un activateur rapide de la troponine du muscle de nouvelle génération -> entraîne une augmentation de la contractilité du muscle

Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early-Stage Amyotrophic Lateral Sclerosis
A Randomized Clinical Trial

Ryosuke Oki, MD; Yuishin Izumi, MD, PhD; Koji Fujita, MD, PhD; Ryosuke Miyamoto, MD; Hiroyuki Nodera, MD, PhD; Yasutaka Sato, MLT; Satoshi Sakaguchi, MD, PhD; Hiroshi Nokihara, MD, PhD; Kazuaki Kanai, MD, PhD; Taiji Tsunemi, MD, PhD; Nobutaka Hattori, MD, PhD; Yuki Hatanaka, MD, PhD; Masahiro Sonoo, MD, PhD; Naoki Atsuta, MD, PhD; Gen Sobue, MD, PhD; Toshio Shimizu, MD, PhD; Kazumoto Shibuya, MD, PhD; Ken Ikeda, MD, PhD; Osamu Kano, MD, PhD; Kazuto Nishinaka, MD; Yasuhiro Kojima, MD; Masaya Oda, MD, PhD; Kiyonobu Komai, MD, PhD; Hitoshi Kikuchi, MD, PhD; Nobuo Kohara, MD, PhD; Makoto Urushitani, MD, PhD; Yoshiaki Nakayama, MD, PhD; Hidefumi Ito, MD, PhD; Makiko Nagai, MD, PhD; Kazutoshi Nishiyama, MD, PhD; Daisuke Kuzume, MD; Shun Shimohama, MD, PhD; Takayoshi Shimohata, MD, PhD; Koji Abe, MD, PhD; Tomohiko Ishihara, MD, PhD; Osamu Onodera, MD, PhD; Sagiri Isose, MD, PhD; Nobuyuki Araki, MD, PhD; Mitsuya Morita, MD, PhD; Kazuyuki Noda, MD, PhD; Tatsushi Toda, MD, PhD; Hirofumi Maruyama, MD, PhD; Hirokazu Furuya, MD, PhD; Satoshi Teramukai, PhD; Tatsuo Kagimura, PhD; Kensuke Noma, MD, PhD; Hiroaki Yanagawa, MD, PhD; Satoshi Kuwabara, MD, PhD; Ryuji Kaji, MD, PhD; for the Japan Early-Stage Trial of Ultrahigh-Dose Methylcobalamin for ALS (JETALS) Collaborators

Vit B12
100 mg/semaine

Key Points

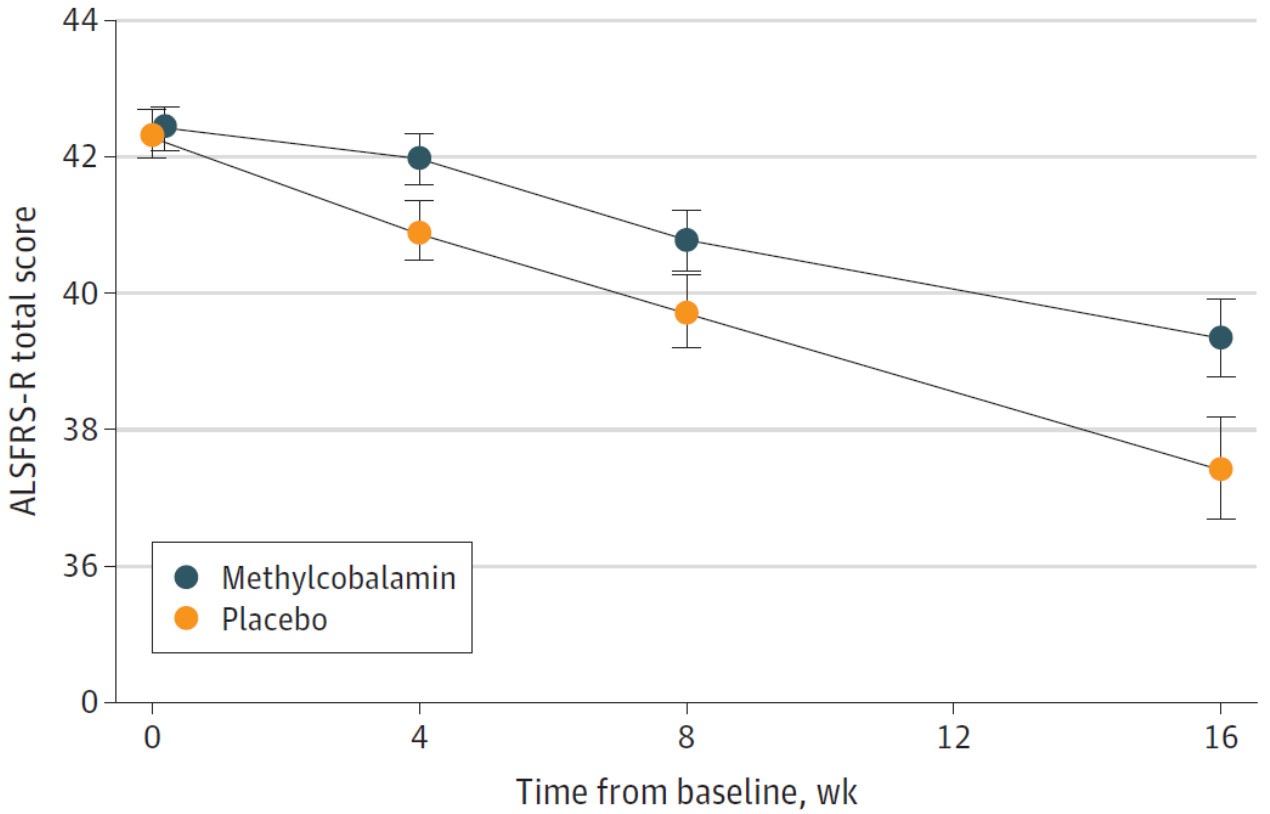
Question Does twice-weekly intramuscular injection of 50-mg ultrahigh-dose methylcobalamin slow clinical progression in early-stage amyotrophic lateral sclerosis?

Findings In this randomized phase 3 clinical trial that included 130 participants who were enrolled within 1 year from symptom onset and presented with a 1- or 2-point decrease on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale total score during 12 weeks of observation, the changes in the score were −2.66 with methylcobalamin vs −4.63 with placebo during the 16-week treatment, which significantly differed.

Meaning Ultrahigh-dose methylcobalamin may slow functional decline in early-stage amyotrophic lateral sclerosis with moderate progression rate.

JAMA Neurol. 2022 Jun 1;79(6):575-583.

Figure 2. Primary Efficacy Outcomes



MEXILETINE FOR MUSCLE CRAMPS IN AMYOTROPHIC LATERAL SCLEROSIS: A RANDOMIZED, DOUBLE-BLIND CROSSOVER TRIAL

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Accepted 25 February 2018

ABSTRACT: *Introduction*: More than 90% of amyotrophic lateral sclerosis (ALS) patients have muscle cramps, but evidence-based treatments have not been available. *Methods*: A multicenter, double-blind, placebo-controlled crossover trial of mexiletine 150 mg twice daily was conducted in ALS patients requesting treatment of symptomatic muscle cramps. *Results*: Muscle cramp frequency was reduced in 18 of 20 patients; 13 reductions were attributed to treatment ($P < 0.05$). The average reduction, based on *t* tests, was 1.8 cramps per day (a reduction from 5.3 with placebo to 3.5 with mexiletine). The estimated reduction of cramp severity was 15 units on a 100-unit scale ($P = 0.01$) from a baseline average of 46. No effect on fasciculations was noted. One patient discontinued the study because of dizziness, and another patient discontinued the study to start open-label mexiletine therapy. No serious adverse event occurred. *Discussion*: Mexiletine is a well tolerated and effective medication for controlling the symptom of muscle cramps in ALS.

Oskarsson B et al. Muscle Nerve. 2018 Mar 6:10.

Mexiletine 150 mg 1-0-1

Petit group (20 patients)

Réduction de nombre et intensité des cramps

«Orphan Drug» approuvé en Europe
pour les maladies myotoniques (Steinert)

Enhanced Bulbar Function in Amyotrophic Lateral Sclerosis: The Nuedexta Treatment Trial

Richard Smith[1] · Erik Pioro[2] · Kathleen Myers[1] · Michael Sirdofsky[3] · Kimberly Goslin[4] · Gregg Meekins[5] · Hong Yu[6,7] · James Wymer[8] · Merit Cudkowicz[6,7] · Eric A. Macklin[6,7] · David Schoenfeld[6,7] · Gary Pattee[9]

Neurotherapeutics. 2017 Jul;14(3):762-772.

- Dextromethorphane 20 mg et quinidine 10 mg
- Phase 2, cross-over design; phase 3 manquante
- Amélioration de la fonction bulbaire, spécifiquement l'amélioration de la parole et de la déglutition, et amélioration de la capacité à traiter les sécrétions orales.
- + effect sur la labilité émotionnelle (pseudobulbar affect) : Pioro EP, Ann Neurol. 2010 Nov;68(5):693-702.

- Disponible uniquement aux États Unis

Vielen Dank fur die Aufmerksemkeit /

Merci beaucoup pour votre attention